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NUCLEAR MEDICINE HYBRID IMAGING (SPECT/CT) IN DISTINGUISHING THE PRESENCE OF A HEPATIC HEMANGIOMA – SINGLE CENTER STUDY

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КОРИШЋЕЊЕ ХИБРИДНОГ СНИМАЊА У НУКЛЕАРНОЈ МЕДИЦИНИ (SPECT/CT) ЗА ОДРЕЂИВАЊЕ ПРИСУСТВА ХЕМАНГИОМА ЈЕТРЕ – СТУДИЈА ЈЕДНОГ ЦЕНТРА

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ABSTRACT

Objective. Hepatic hemangioma (HH) is the most common benign liver tumor, and the second most frequent tumor in the liver after hepatic metastasis. The SPECT/CT hybrid technique will be beneficial for the investigation of this type of HH since it can precisely identify the hepatic lesions. The aim of this study was to reevaluate the sensitivity and specificity of the nuclear medicine method for confirmation or exclusion of benign hemangioma of the liver based on a series of cases at our department and briefly review the literature.

Methods. We retrospectively analyzed 107 patients, 62 females (57.94%) and 45 males (42.05%) with mean age 50.05±11.92 years, referred to the Nuclear Medicine Department for 99mTc-RBC scintigraphy of the liver to conclude or exclude the presence of HH, in the period 2019 to 2020.

Results. Hepatic scintigraphy located the hemangiomas mostly in the right hepatic lobe. The size of the lesion varied from to 6-140 mm (46.04 ± 27.1); 13 hemangiomas were described as giant. SPECT-CT confirmed HH in 1 patient that was negative on ultrasound, besides 30/87 (34.48%) patients who were described as positive on US and turned out to be negative on the scintigraphic method. In 53 (60.92%) patients, positive matching of the US images and hybrid SPECT/CT imaging for HH was found. Most of the patients had benign referral diagnosis, while 12 of them had confirmed malignant diagnosis in whom eight (n=8, 66.67%) were confirmed free of hepatic metastasis and SPECT-CT detected HH, while in 4 patients who were described as positive for HH on the CT scan, the scintigraphic method excluded HH and further evaluation of the hepatic lesion was needed.

Conclusion. Hepatic hemangiomas require a careful diagnosis to differentiate from other focal hepatic lesions, co-occurring diagnoses are also possible. Differentiating between HH and hepatic metastatic disease is a typical clinical difficulty when the problem is present in staging or monitoring patients with oncological disease.

Key words: *hemangioma; single photon emission computed tomography computed tomography; scintigraphy; ultrasonography.*

САЖЕТАК

Увод. Хемангиом јетре је најчешћи бенигни тумор јетре и други по учесталости тумор после метастаза у јетри. SPECT/CT хибридна техника корисна је за испитивање овог типа хемангиома јер може прецизно идентификовати лезије јетре. Циљ овог истраживања био је да се на основу низа случајева на нашем одељењу поново процене осетљивост и специфичност нуклеарномедицинске методе за потврду или искључење бенигног хемангиома јетре, као и кратак преглед литературе.

Методе. Урађена је ретроспективна анализа 107 пацијената, 62 жене (57,94%) и 45 мушкараца (42,05%), просечне старости 50,05 ± 11,92 године, упућених на Одељење за нуклеарну медицину на 9 mTc-RBC сцинтиграфију јетре да би се утврдило или искључило присуство хемангиома јетре, у периоду од 2019. до 2020. године.

Резултати. Сцинтиграфијом јетре лоцирани су хемангиоми, углавном у десном режњу јетре. Величина лезије варирала је од 6 мм до 140 мм (46,04 ± 27,1); 13 хемангиома описано је као џиновско. SPECT/CT је код једног пацијента, који је био негативан на ултразвуку, потврдио хемангиом јетре, док је код 30/87 (34,48%) пацијената који су на УЗ описани као позитивни сцинтиграфска метода показала да су негативни. Код 53 (60,92%) пацијента пронађено је позитивно подударање УЗ снимака и хибридног SPECT/CT снимања за хемангиом јетре. Већина пацијената је имала бенигну упутну дијагнозу, док је код њих 12 потврђена малигна дијагноза, код којих је (n = 8, 66,67%) потврђено да нема метастаза у јетри и SPECT/CT детектованог хемангиома јетре, док је код четири пацијента позитивна на хемангиом јетре на ЦТ скенирању сцинтиграфска метода искључила хемангиом јетре те је била потребна даља евалуација лезије.

Закључак. Хемангиоми јетре захтевају пажљиву дијагнозу да би се разликовали од других фокалних лезија јетре, а могуће су и истовремене дијагнозе. Разликовање између хемангиома јетре и хепатичне метастатске болести типична је клиничка тешкоћа када постоји проблем у одређивању или праћењу пацијента са онколошким обољењем.

Кључне речи: *хемангиом, једнофотонска емисиона компјутерска томографија, сцинтиграфија, ултрасонографија*

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INTRODUCTION

Hepatic hemangioma (HH) is the most common benign liver tumor and the second most frequent tumor in the liver after hepatic metastasis. It usually presents as a single tumor appearance, but multiple hemangiomas can also be detected. Commonly they are located in the right lobe, while in 40% of the cases, they may appear in both lobes (1). The incidence of these liver masses ranges from 2% to 7% of all liver lesions (2). They are more prevalent in women, most likely due to the impact of female sex hormones on their growth, especially in women with a history of multiparity (3). The female to male ratio reported in literature varies from 3-6:1(4).

Clinicians often encounter a diagnostic dilemma of whether the detected hepatic lesion/mass is a benign or malignant tumor. Hemangiomas, or hemangioma-like appearing lesions, are frequently detected in the liver often as an incidental finding on ultrasound (US) or when using cross-sectional imaging - computed tomography (CT) or magnetic resonance imaging (MRI) (5). Many diagnostic methods are used in clinical practice for detection of HH, with the US being the most valuable, cheapest and easiest to perform method, but due to the lack of specificity of ultrasound findings further imaging tests are necessary to establish the diagnosis.

CT is also used in distinguishing different hepatic lesions, with accent to oncologic patients, where hepatic metastasis cannot be excluded. Hepatic hemangiomas on CT scan usually appear hypodense on unenhanced images. After intravenous administration of contrast medium, HH shows a characteristic enhancement pattern, with early peripheral nodular enhancement, coupled with centripetal forces of the lesion at different stages (6). While magnetic resonance imaging (MRI) is often regarded as the gold standard, its accessibility is limited, and its high cost means that it is rarely the first method of choice. Additionally, certain medical conditions, exclude the use of MRIs. Hemangiomas have a characteristic MRI appearance in most cases, as well-defined lesions, which are homogeneous with high T2- signal, the “cotton-wool” aspect (7). Contrast-enhanced MRI and CT have limited capabilities to differentiate focal hepatic lesions (8, 9).

The diagnosis of a HH almost never requires a biopsy. Early studies on fine-needle aspiration (FNA) of a liver hemangioma showed a considerable risk of bleeding complications, which are sometimes fatal (10, 11). The SPECT/CT hybrid technique will be beneficial for the investigation of this type of HH since it can precisely identify the hepatic lesions. It is possible to avoid other more invasive procedures like biopsy by using the non-invasive and highly specific technique of scintigraphy with radiolabeled red cells using 99mTc via SPECT (12). The aim of this study was to reevaluate the sensitivity and specificity of the nuclear medicine method for confirmation or exclusion of benign hemangioma of the liver based on a series of cases at our department and briefly review the literature.

MATERIALS AND METHODS

We retrospectively analyzed 107 patients, 62 females, (57.94%) and 45 males (42.05%) with mean age 50.05±11.92 years, referred to the Nuclear Medicine Department for 99mTc-RBC scintigraphy of the liver to conclude or exclude the presence of HH, in the period 2019 to 2020. Inclusion criteria – patients of both gender, over 18 years of age, with accidentally detected hepatic lesion either on US, or with CT suspected for hemangiomas; Exclusion criteria – pregnancy and breastfeeding females, patients with previously confirmed hepatic metastasis.

Procedure

SPECT/CT of the liver was performed with in vivo method with intravenously (i.v) administration of stannous pyrophosphate, and 30 min after, we injected i.v 550MBq $^{99m}TcO_4$. SPECT/CT for hemangioma detection that was performed two hours post injection, according to the following acquisition protocol:

- SPECT scan (60 projections for 15 seconds per projection, angle per projection: 3 degrees, angle per detector: 180 degrees, number of views: 120 step and shoot mode, matrix 128*128, zoom 1.0). The SPECT was equipped with a low-energy high-resolution collimator. The energy peak was 140 keV, the width of the energy window was from 15% to 20%.
- CT scan (matrix 512*512, rotation time: 1 second, section thickness: 2.5mm, distance between sections 2.5mm). SPECT/CT camera OPTIMA NM/CT 640 GE Healthcare dual detector / 4 slice CT was used for patient scanning.

Image analysis

The SPECT images were reconstructed from the raw data by iterative reconstruction by applying a Butterworth filter whose critical frequency was 0.48, without applying motion correction. The CT data were reconstructed using a nuclear medicine workstation. Then the matching emission and transmission scans were fused to form the fusion images. All images were retrospectively evaluated by 3 nuclear medicine physicians independently for the presence of HH. Furthermore, localization, number of HH and the size of lesions were also noted.

Data analysis

Patient characteristics and data from nuclear medicine images and the other diagnostic methods were analyzed

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using descriptive statistics. The detection rate of HH in SPECT/CT images was calculated as the ratio between the number of patients with at least 1 detected HH in a nuclear medicine image and the total number of patients in the study.

RESULTS

Some patients had only US, others only CT, and some acquired both. 87 patients (81.31%) had an ultrasound; 83 of them had positive results for HH, whereas 4 had negative results. Out of 74 patients (69.16%) who underwent CT examination, 63 were found positive for HH, 2 were described as metastasis, 2 as cystic lesions, 4 as non-defined lesions and 1 as focal nodular hyperplasia.

More than half of the patients (n=66, 62.26 %) had one lesion only, while two or more lesions were seen on ultrasound or CT in (n=36, 33.96%). Ultrasound demonstrated hyperechoic lesion. In some cases, mixed echogenicity was seen, while CT scans described mostly hypodense liver lesions, (Table 1).

Hepatic scintigraphy located the hemangiomas mostly in the right hepatic lobe, (Table 2). The size of the lesion varied from 6 to 140 mm (46.04 ± 27.1); 13 hemangiomas were described as giant. A case of a giant hemangioma with increased uptake of the tracer and central necrosis (photogenic defect) is presented in Figure 1.

SPECT-CT confirmed HH in 1 patient that was negative on ultrasound, while excluded HH in 30/87 (34.48%) patients who were described as positive on US. In 53 (60.92%) patients, positive matching of the US images and hybrid SPECT/CT imaging for HH was found, while in 3 patients we confirmed negative matching (Table 3).

Most of the patients had benign referral diagnosis, while 12 of them had confirmed malignant diagnosis in whom (n=8, 66.67%) were confirmed free of hepatic metastasis. We show confirmation of a hepatic hemangioma on the hepatic scan in an oncologic patient with breast cancer, where we excluded hepatic metastasis (Figure 2). SPECT-CT detected hepatic hemangioma, while in 4 patients who were described as positive for HH on the CT scan, the scintigraphic method excluded HH and further evaluation of the hepatic lesion was needed.

DISCUSSION

Hepatic hemangiomas are usually incidentally diagnosed when patients undergo imaging tests or other procedures for purposes other than evaluating a hepatic mass. Sometimes they may present upper abdominal pain because of the distension of Glisson's capsule. Most of these benign hepatic masses are asymptomatic and simply need to be monitored, consisting of clusters of blood-filled cavities lined by endothelial cells and fed by the hepatic artery (13). The etiopathogenesis of HH is not completely understood. They are postulated to be vascular malformations or hamartomas of congenital origin that undergo enlargement by ectasia, rather than by

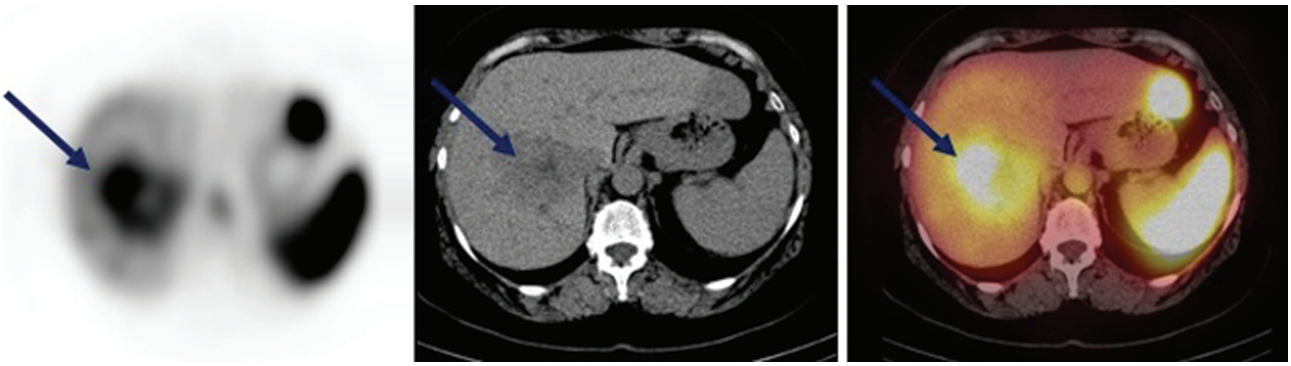

Figure 1

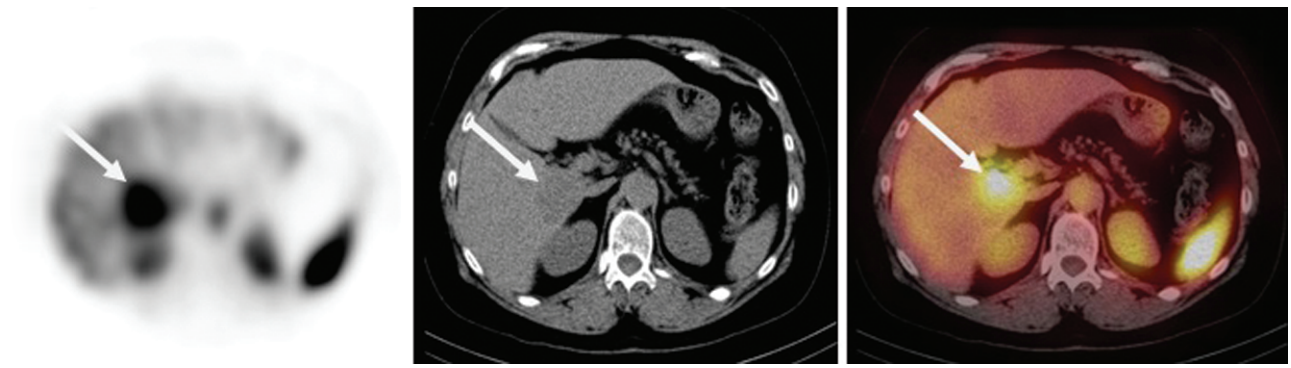

Figure 2

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Table 1: Ultrasound and CT findings

Ultrasound echogenicity (n= 87 patients; no data for 24 patients)			
Cystic lesion 1 (1.59%)	Isoechoic 4 (6.35%)	Hypoechoic 17 (26.98%)	Hyperechoic 41 (65.07%)
Number of hepatic lesions seen on US or CT (n =106 patients, no data for 1 patient)			
1 lesion 66 (62.26%)		More than 1 lesion 36 (33.96%)	No lesion detected 4 (3.77%)

US = ultrasound; CT = computed tomography

Table 2: SPECT/CT scintigraphy findings

Hepatic lobe that was affected (n=102, no data for 5 patients)	left lobe 17 (16.67%)
	right lobe 77 (75.49%)
	both lobes 5 (4.90%)
Hepatic segment that was affected	segment 2 (5 patients)
	segment 3 (7 patients)
	segment 4 (8 patients)
	segment 5 (11 patients)
	segment 6 (16 patients)
	segment 7 (24 patients)
	segment 8 (11 patients)
Hepatic scintigraphy findings	positive findings 68
	negative findings 39

Table 3: Matching of the two methods (US and SPECT/CT)

	US positive	US negative
SPECT/CT positive	53/87 (60.92%)	1/87 (1.15%)
SPECT/CT negative	30/87 (34.48%)	3/87 (3.45%)

US = ultrasound; SPECT = single photon emission computed tomography

hypertrophy or hyperplasia (14). It is important to distinguish HH from other benign and malignant liver lesions. Benign lesions include cysts, adenomas, regenerating nodules, focal nodular hyperplasia, and abscesses, and malignant lesions include hepatocellular carcinoma, hepatic angiosarcoma and hepatic metastases (15).

The unique role in the evaluation of hepatic masses plays the nuclear medicine scintigraphic method, using autologous radiolabeled red blood cells 99mTc-RBC, making this method an initial diagnostic examination. The method was first described in the 1980s, and since then has become a modality of choice for confirmation of HH and has not been exceeded by other radiological methods, with the exception of MRI (16). This imaging is non-invasive, economical, easily performed and a highly specific method for detection of HH. Cases of angiosarcoma have been described differentially, as a very rare cause of a false-positive finding, but with combination with SPECT/CT the method has a nearly 100% positive predictive value (17). Correspondingly, most of the 99mTc-RBC scan positive cases, require only follow up without further treatment, whereas negative cases require further evaluation for definite diagnosis and clinical management. The scintigraphic method gives characteristic pattern for diagnosing HH, with initial hypoperfusion followed by a gradual accumulation of activity, giving the so-called "perfusion-blood pool mismatch" pattern (18). In spite of the guidelines for hemangioma that recommend including initial flow images, it is not routinely performed at our department, as the delayed phase combined with SPECT/CT is the most accurate one (19).

HH are usually mono-lesions, but multiple-lesions can occur; depending on the source, they can make up 2.3% to up to 20–30% of cases (13). In our study more than half of the patients (n=66, 62.26%) had one lesion only, while two or more lesions were seen on ultrasound or CT in (n=36, 33.93%). Ultrasound demonstrated hyperechoic lesion. In some cases, mixed echogenicity was seen, while CT scans described mostly hypodense liver lesions.

Our study revealed that the majority of the hemangiomas were found in the right hepatic lobe, similar to literature data (20). The size of the lesion varied from to 6-140 mm (46.04 ± 27.1); 13 hemangiomas were described as giant. The most affected segment was number 7, followed by segment number 6 and then segment 5 and 8.

In the literature, the sensitivity rate for 99mTc-RBC scans varied between 70% and 85%, whereas the specificity rate was 100%. Sensitivity and specificity rates in the study of El-Desouki M et al. were 100% and 89%, respectively. The accuracy rate resulted in 98.6%. Only a single resulted false positive and it was a hepatocellular carcinoma (21).

Regarding the dimensions, the smallest are the capillary hemangiomas, which range in size from a few mm to 3 cm, medium sized hemangiomas from 3 cm to 10 cm, that are well-defined lesions requiring follow-ups only, and the giant hemangiomas, which can reach 10 cm or more that may require therapy or surgical intervention. Yilmaz and coworkers found a sensitivity of 92% due to 5 false negative cases that were small in size or close to the large liver vessels (22). The sensitivity of 99mTc-RBC scintigraphy is firmly size-related with a cut off between 1 and 2 cm, with larger lesion being diagnosed 100% (13).

Sensitivity is greatly influenced by size, especially at the small end of the range: 17–20% for lesions under 1 cm in size, 65–80% for lesions between 1 cm and 2 cm, and practically 100% for lesions greater than 2 cm. Over the entire size range, SPECT using Tc-99m labeled RBC scintigraphy maintains 100% specificity (13).

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Schillaci et al reported four (33.3%) of 12 patients evaluated in the study, fusing SPECT/CT added significant information to SPECT alone, enabling accurate diagnosis in 16.7% of the lesions. Hence, SPECT/CT increased the accuracy of scintigraphy of 99mTc-RBC, in classifying hepatic lesions such as hemangiomas or non-hemangiomas, from 70.8% (17/24) to 87.5% (21/24) (23).

Very large hemangiomas may seem more heterogeneous on CT or MRI than smaller hemangiomas do. This is typically caused by severe hyalinization, thrombosis, fibrosis, or bleeding. Such tumors are more difficult to diagnose with cross-sectional imaging modalities (8). As reported by Jian-Guo Zheng et al., 8 out of the 31 patients who were investigated (or 25.81%) had anatomically unfavorable localization of HH. Three of them had hepatic lesions that were close to the abdominal aorta, four had lesions that were close to the inferior cava, and one had a hemangioma that was close to the heart (2).

For further assessment of atypical or equivocal findings a semi-quantitative analysis of SPECT/CT can be conducted with drawing region of interest above the suspected hemangioma lesion (HEM), the heart and uninvolved liver tissue, and calculated the ratios afterwards. The authors that proposed this algorithm found a HEM/liver ratio higher than 1.6 indicative for HH (24).

When the anatomical position of the HH is not ideal, the functional information obtained from SPECT along with anatomical information from CT can assist in resolving the dilemma. CT scan can precisely locate the region of increased focal radioactivity (the lesion), and finally to diagnose HH (9).

In conclusion, Hepatic hemangiomas require a careful diagnosis to differentiate from other focal hepatic lesions, co-occurring diagnoses are also possible. The clinical value of this scintigraphic method is well established, especially in cases where CT and US are equivocal. The usefulness of scintigraphy with radiolabeled autologous erythrocytes lies in high safety rate, its high specificity and positive predictive value for confirming HH.

In patients with known hepatic masses, although it has a characteristic appearance on US or CT by contrast, confirming the HH with this hybrid scintigraphic method (SPECT/CT), can facilitate the care not only of the patient but also help solve the diagnostic dilemma of the clinicians and avoid further unnecessary and expensive diagnostic testing. Additionally, making a diagnosis from cross-sectional images of a significant number of atypical hepatic hemangiomas is challenging. Differentiating between HH and hepatic metastatic disease is a typical clinical difficulty when the problem is present in staging or monitoring patients with oncological disease.

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